REMARKS

Replacement of Drawing Sheets

Applicants have included herewith replacement drawing sheets that now meet all requirements of 37 CFR §1.84.

Rejection of Claims and Traversal Thereof

In the July 2, 2002 Office Action,

claims 1-12 were rejected under 35 U.S.C. §112, first paragraph; and

claims 1-6 and 10-12 were rejected under 35 U.S.C. §112, second paragraph.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

In the July 2, 2002 Office Action, claims 1-6 and 10-12 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

According to the Office, the disclosure fails to provide adequate guidance in a number of areas. As such, applicants will address each of the Office's remarks and contentions individually.

1. The Office contends that "Applicants have not provided guidance in the specification toward specific treatment protocols or a pharmaceutical composition containing a chemotherapeutic agent and AAV-2 that would show AAV-2 infection is capable to reduced radiotherapy or chemotherapy-induced

tumor resistance in patients." In response, applicants argue that ample disclosure has been provided in the instant application for practicing the present invention. For instance, on page 4, line 18 to page 5, line 22 of the amended specification submitted herewith, there is a complete discussion on methods for administration of the AAV-2 virus. The AAV-2 virus can be administered in a physiological common salt solution, Ringer's solution or PBS solution. The effective amount of the virus dose employed is defined to include 10^9 - 10^{10} AAV-2 particle/kg body weight. Clearly, one skilled in the art would recognize that the amount of the chemotherapeutical agent can be determined by a physician and is dependent on the patient's sex, weight, severity of the disease, kind of administration and planned duration of administration. A pharmaceutical composition including both chemotherapeutical agent and AAV-2 is described specifically in lines 8-14 on page 5. Thus, one skilled in the art without the exercise of inventive skill or undue experimentation could determine an effective dose, especially because the disclosed chemotherapeutical agents are well known in the art and have been used for many years to treat cancers.

2. According to the Office:

> "Although the specification discloses that co-administration of AAV-2 with chemotherapeutic agents to xenografted mouse model stop and reverse tumor growth in otherwise chemo-resistant tumor, whether it will stop and reverse tumor growth in a cancer patient is unpredictable due to the different environment the tumor resides."

The Office then cited an article[2] by Gura that discussed the unpredictability of using a mouse model. However, the Office selectively chose only a section of the Gura article, when in fact the article further states at page 1042, column 1, that:

> "The limitation of animal models have spurred the NCI, among others, to test drug candidate in cultures of human cells. The institute now relies on a panel of 60 human cells, including samples of all the major human malignances. Drugs to be tested are fed to subsets of the panel, based on tumor cell type, and their cell-killing activity is monitored."

Thus, it is evident that the NCI, cited as an authority by the Office, also considers the use of cancer cells as an appropriate and applicable testing method to augment nude mouse testing for cancer treatments. As the Office has already agreed, applicants not only include data, in the present specification, showing the

[2] Gura, Trisha, System for Identifying New Drugs Are Often Faulty, *Science,* Vol. 276, November 7, 1997.

effectiveness of applicants' method in the mouse model but also in the small cell lung cancer cell lines. Thus applicants have gone the extra step recommended by NCI.

After reviewing the Office Action of July 2, 2002, applicants are very concerned by the lack of continuity in the examination of applicants' application when compared to other applications that have been issued as patents and relate to methods for cancer treatment. Applicants want to draw the Office's attention to the plurality of patents that have issued in the period after the 1997 filing date of present invention (and the publication of the Gura article) relating to cancer treatment. It should be noted that each of the patents discussed below include, as proof of concept, testing methods limited to cancer cell testing and/or nude mouse testing (there are no human test results). Applicants have included in Appendix C all patents discussed herein below. Applicants could have cited numerous other cancer treatment patents that were found allowable. However, to avoid redundancy the following group of patents should be sufficient to show that both cancer cell lines and nude mouse testing are considered acceptable testing regimes to show efficacy of a cancer treatment (as cited by the Gura article). Evidence of this fact is presented in the following issued patents.

1. **U.S Patent No. 6,414,325**, entitled "COMPOUNDS AND METHODS FOR CANCER THERAPY" filed in 1999 and issued on July 9, 2002, Primary Examiner Avis M. Davenport.

   Allowed claim for cancer treatment:

   Claim 1

   > A method for treating a cancer in a mammal, comprising administering to a mammal a cell adhesion modulating agent that comprises the sequence HAV within a cyclic peptide ring, and thereby treating the cancer in the mammal.

   Test Results

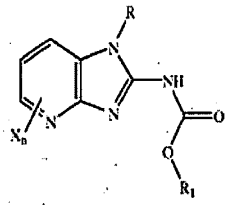
   Tests conducted include cancer cell lines and Example 8 specifically includes test results from nude mouse model. There are no human tests results.

2. **U.S Patent No. 6,384,049,** entitled "CANCER TREATMENT" filed 2000 and issued on May 7, 2002, Primary Examiner Frederick Krass..

Allowed claim for cancer treatment:

Claim 1

A method for treating cancer comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising a pyridinylimidazole carbamate of the formula:



wherein
X is independently selected from the group consisting of hydrogen halo, hydroxyl, alkyl of less than 8 carbon atoms and alkoxy of less than 8 carbon atoms;
n is a positive integer less than 4; and
R and R_1 are independently selected from hydrogen, or an alkyl group of from 1 to 8 carbons,
Or a pharmaceutically acceptable salt thereof, or a prodrug thereof.

Test Results

Example 1 includes test results from a nude mouse model. There are no cell test results or human tests results.

3. **U.S Patent No. 6,342,483,** entitled "METHOD FOR DETECTION AND TREATMENT OF BREAST CANCER" filed in 1998 and issued on January 29, 2002, Primary Examiner Nguyen and Assistant Examiner Nguyen.

Allowed claim for cancer treatment:

Claim 1

A method for suppressing the growth of a sporadic epithelial breast tumor in a mammal, the method comprising infusing directly to said sporadic tumor a vector comprising a BRAC1 nucleic acid sequence encoding a BRCA1 protein having tumor suppressor activity, the nucleic acid sequence operatively linked to a promoter, wherein

production of the BRCA1 protein results in a decrease in the growth rate of said epithelial breast tumor.

Test Results

There are no actual tests conducted in this patent, but instead only prophetic examples. There are no human tests results.

4. **U.S Patent No. 6,331,284,** entitled "P202 IS A TUMOR SUPPRESSOR" filed in 2000 and issued on December 18, 2001, Primary Examiner David Guzo.

Allowed claims for cancer treatment:

Claim 1

A method for repressing transformation in a cell, the method comprising contacting said cell with a p202 polypeptide in an amount effective to inhibit a transformed phenotype.

Claim 9

The method of claim 1, wherein the cell is in an animal.

Claim 23

The method of claim 9, wherein said animal is a human.

Test Results

Tests conducted include cancer cell lines and Example 8 specifically includes test results from nude mouse model. There are no actual human tests conducted but there is a long lengthy prophetic example described for conducting clinical tests in the future.

5. **U.S Patent No. 6,319,493,** entitled "TREATMENT OF NEOPLASTIC DISEASE WITH INTERLEUKIN-10" filed in 2000 and issued on November 20, 2001, Primary Examiner Prema Mertz.

Allowed claims for cancer treatment:

Claim 1

A method of reducing the growth of a tumor cell in a mammal, comprising administering a therapeutically effective amount of interleukin-10 to the mammal.

Test Results

Tests conducted include cancer cell lines and Example 8 specifically includes test results from a BALC/c mouse model. There are no actual human tests conducted but there is a long lengthy prophetic example described for conducting clinical tests in the future.

6. **U.S Patent No. 6,297,230,** entitled "CYANOAZIRIDINES FOR TREATING CANCER" filed in 1998 and issued on October 2, 2001, Primary Examiner Taofiq Solola.

Allowed claims for cancer treatment:

Claim 1

> A method of treating cancer, wherein the cancer is selected from the group comprising multiple myeloma, a β-lymphocyte plasmacytoma, advanced stage ovarian epithelial cell cancer, metastatic melanoma, leukemia of lymphoid and nonlymphoid origin, metastatic colon cancer, breast cancers and metestatics lung cancers, by administering to a patient in need of treatment an a unit dose of a compound of formula in claim 1 ...

Test Results

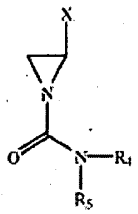
As stated in Example 20, in vitro tests were conducted in tumor cells and in vivo survival studies in mice. There are no actual human tests conducted but there is a long lengthy prophetic example described for conducting clinical tests in the future.

7. **U.S Patent No. 6,245,807,** entitled "TREATMENT OF HUMAN PROSTATE DISEASE" filed in 1998 and issued on June 12, 2001, Primary Examiner Ardin H. Marschel.

Allowed claims for cancer treatment:

Claim 1

A method of treating androgen independent prostate cancer in a human comprising: selecting a human having androgen independent prostate cancer, and administering to said human an effective amount of a compound of the following formulae I or II to stimulate prostate cell death:



wherein R and R_1 are each independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl (SH), halogen, substituted alkyl, unsubstituted alkyl, substituted alkenyl, unsubstituted alkenyl, substituted aryl, unsubstituted aryl, substituted alkoxy unsubstituted alkoxy, and salts thereof, wherein the dotted double bond between the ring carbons to which R and R1 are bonded represent an optimal ring double bond.

Test Results

Tests conducted include cancer cell lines and Example 5 specifically includes test results from nude mouse model. There are no human tests results.

Clearly, the fact that the above discussed patents issued is proof that the respective specifications provided sufficient guidance to meet the 112 disclosure requirements by including test results from cancer cells and the nude mouse model. Applicants have also met this standard by including test results in several different methods as found acceptable by the NCI as stated in the article cited by the Office. Applicants not only provided *in vitro* data in Examples 1 and 2 but also showed that the *in vitro* data was predictive for *in vivo* utility and efficacy in Example 3. Test data resulting from tests performed on the nude mouse model provide actual evidence that applicants' claimed invention enhanced sensitivity of small cell lung cancer cells (SCLC) and reversed chemotherapy-resistance when chemotherapeutic agent were combined with AAV-2 infection. As shown in Figure 3, treatment with the chemotherapeutics resulted in a rapid decrease in tumor volumes and complete regression after 3 weeks of treatment. The combination of chemotherapy with AAV-2 infection led to a more pronounced decline of tumor volume

compared with animals that received only chemotherapy, indicating a sensitization of drug-treated tumor cells. Treatment was interrupted after regression of the tumors and was resumed when relapses occurred. Treatment of recurrences was less efficient in animals that received only drug treatment but when treated with AAV-2, the resistance to treatment was completely reversed. Tumors treated with the combination had completely regressed in comparison to the tumors treated with just the chemotherapeutic drug.

The claims as now amended recite applicants' invention in terms fully supported in the disclosure defining the subject matter sought to be patented. The claims thus are in compliance with the enablement requirement of the first paragraph of section 112. Applicants respectfully request the withdrawal of the rejection of claims 1-12 under §112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-6 and 10-12 were rejected under 35 U.S.C. §112, second paragraph. Applicants have amended the claims according to the suggestion of the Examiner. As such, the amendment of claims 1-6 and 10-15 obviates the rejection under §112, and as such applicants request the withdrawal of this rejection.

Personal Interview

If Examiner Qian maintains the 112 rejections, applicants would like the opportunity to discuss the present invention with Examiner Qian and her Supervisory Examiner Yucel, especially in light of the fact that applicants have met the standards of providing sufficient testing results according to 112 requirements and further have provided results from suggested testing methods described in the Gura article. Further the testing methods used by applicants were found acceptable by the USPTO as evidenced by the issued patents discussed herein.

Fees Payable

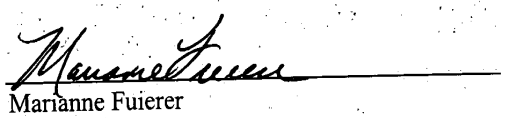
One new independent claim and two dependent claims have been added beyond the number for which a fee has previously been paid, resulting in an added claims fee of $69.00. A check in the amount of $69.00 is submitted herewith in payment of the fee for the additional claims. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this

amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

CONCLUSION

Pending claims 1-15 meet all requirements of patentability and are in condition for allowance. If any issues remain outstanding, incident to allowance of the application, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss their resolution, in order that this application may be passed to issue at an early date.

Respectfully submitted,



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APPENDIX A

Version with Markings to Show Changes Made

In the Claims:

Please amend claims 1, 5 and 10 as follows:

1) A method for lowering [the] chemotherapy-induced resistance in a patient being treated with a chemotherapeutic agent for a cancer, the method comprising:

infecting the patient with an effective amount of AAV-2 to lower the chemotherapy-induced resistance to the chemotherapeutic agent, in combination with administering a chemotherapeutic agent patient; and

determining if the chemotherapy-induced resistance to the chemotherapeutic agent is lowered.

5) The method according to any of claims 1 to 4, wherein the AAV-2 is administered [use is made] intravenously, cutaneously, orally or intratumorally.

10) A method for reversing chemotherapy-induced resistance in a patient suffering from a small cell lung carcinoma cancer and previously treated for the cancer by a chemotherapeutic agent selected from the group consisting of cisplatin, etoposide and cisplatin/etoposide, the method comprising:

infecting the patient with a sufficient amount of AAV-2 to reverse the chemotherapy-induced resistance to the chemotherapeutic agent, in combination with administering the chemotherapeutic agent to the patient; and

determining if the chemotherapy-induced resistance to the chemotherapeutic agent is reversed.

APPENDIX B

Clean Copy of All Pending Claims

1) A method for lowering chemotherapy-induced resistance in a patient being treated with a chemotherapeutic agent for a cancer, the method comprising:

infecting the patient with an effective amount of AAV-2 to lower the chemotherapy-induced resistance to the chemotherapeutic agent, in combination with administering a chemotherapeutic agent patient; and

determining if the chemotherapy-induced resistance to the chemotherapeutic agent is lowered.

2) The method according to claim 1, wherein the AAV-2 is used in a dose of 10^9 - 10^{10} AAV particles/kg body weight.

3) The method according to claim 1 wherein the chemotherapeutic agent is selected from the group consisting of: cisplatin, etoposide and cisplatin/etoposide.

4) The method according to any of claims 1 to 3, wherein the cancer to be treated by chemotherapy is a colon cancer, pancreatic carcinoma or brain tumor or small cell lung carcinoma.

5) The method according to any of claims 1 to 4, wherein the AAV-2 is administered intravenously, cutaneously, orally or intratumorally.

6) The method according to any of claims 1 to 5, wherein the infecting with the AAV-2 is made before, after or simultaneously with a chemotherapy or radiotherapy.

7) A pharmaceutical composition containing a chemotherapeutic agent and an effective dose of AAV-2 to reverse chemotherapy-induced resistance in patients suffering from small cell lung carcinoma.

8) The pharmaceutical composition according to claim 7, wherein the chemotherapeutic agent is selected from the group consisting of: cisplatin, etoposide and cisplatin/etoposide.

9) The pharmaceutical composition according to claim 7 or 8, wherein the composition is formulated in a member selected from the group consisting of; an injection solution, infusion solution, an aerosol spray or an ointment.

10) A method for reversing chemotherapy-induced resistance in a patient suffering from a small cell lung carcinoma cancer and previously treated for the cancer by a chemotherapeutic agent selected from the group consisting of cisplatin, etoposide and cisplatin/etoposide, the method comprising:

infecting the patient with a sufficient amount of AAV-2 to reverse the chemotherapy-induced resistance to the chemotherapeutic agent, in combination with administering the chemotherapeutic agent to the patient; and

determining if the chemotherapy-induced resistance to the chemotherapeutic agent is reversed.

11) The method according to claim 10, wherein the AAV-2 is administered at a dose of 10^9 - 10^{10} AAV particles/kg body weight.

13) A method for reversing chemotherapy-induced resistance in a cancer cell previously treated for the cancer by a chemotherapeutic agent, the method comprising:

infecting the cancer cell with a sufficient amount of AAV-2 to reverse the chemotherapy-induced resistance to the chemotherapeutic agent, in combination with administering the chemotherapeutic agent to the cancer cell; and

determining if the chemotherapy-induced resistance to the chemotherapeutic agent is reversed.

14) The method according to claim 13, wherein the chemotherapeutic agent comprises an agent selected from the group consisting of: cisplatin, etoposide and cisplatin/etoposide.

15) The method according to any of claims 14, wherein the cancer cell is a colon cancer cell, pancreatic carcinoma cell, brain tumor cell or small cell lung carcinoma cell.